Complete Summary

GUIDELINE TITLE

Practice guidelines for the management of cryptococcal disease.

BIBLIOGRAPHIC SOURCE(S)

Saag MS, Graybill RJ, Larsen RA, Pappas PG, Perfect JR, Powderly WG, Sobel JD, Dismukes WE. Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. Clin Infect Dis 2000 Apr;30(4):710-8. [37 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Cryptococcal disease (Cryptococcus neoformans infection)

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Infectious Diseases
Internal Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To review the choice of treatment and management for disease caused by Cryptococcus neoformans infection depending on:

- Anatomic sites of involvement
- Host´s immune status

TARGET POPULATION

Patients with cryptococcal disease (Cryptococcus neoformans infection)

INTERVENTIONS AND PRACTICES CONSIDERED

Pharmacotherapy

- Amphotericin B
- Lipid formulation of amphotericin B
- Fluconazole
- Itraconazole
- Flucytosine

Other treatments

- Radiographic imaging before lumbar puncture to identify mass lesions that may contraindicate lumbar puncture
- Lumbar puncture
- Medical therapy
- Lumbar drainage
- Ventriculoperitoneal shunt
- Corticosteroids (not recommended for HIV-infected patients)

MAJOR OUTCOMES CONSIDERED

1. Resolution of symptoms (such as cough, shortness of breath, sputum production, chest pain, and fever)
2. Resolution or stabilization of abnormalities (such as infiltrates, nodules, or masses) on chest radiograph
3. Resolution of central nervous system (CNS) abnormalities (such as fever, headache, altered mental status, ocular signs, intracranial pressure, and meningeal signs)
4. Resolution of lesions

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Grades reflecting the quality of evidence on which recommendations are based:

I. Evidence from at least one properly randomized, controlled trial
II. Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), from multiple time-series studies, or from dramatic results of uncontrolled experiments
III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not applicable

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Opinion regarding optimal treatment was based on personal experience and information in the literature. The relative strength of each recommendation was graded according to the type and degree of evidence available to support the recommendation (see the "Rating Scheme for the Strength of the Recommendations" field). The panel conferred in person (on 2 occasions), by conference call, and through written reviews of each draft of the manuscript.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Strength of recommendation:

A. Good evidence to support a recommendation for use
B. Moderate evidence to support a recommendation for use
C. Poor evidence to support a recommendation

D. Moderate evidence to support a recommendation against use
E. Good evidence to support a recommendation against use

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Excerpted by the National Guideline Clearinghouse (NGC)

Each recommendation includes a ranking for the strength and the quality of evidence supporting it. Definitions of the levels of evidence (I-III) and grades of recommendation (A-E) are repeated at the end of the Major Recommendations field.

Guidelines for the Treatment of Cryptococcosis in Patients without human immunodeficiency virus (HIV) Infection

Pulmonary and Non-Central Nervous System Disease

Specific recommendations for the treatment of non–human immunodeficiency virus (HIV)-associated cryptococcal pulmonary disease are summarized in Table 1 of the original guideline document. Regardless of the treatment chosen, it is imperative that all patients with pulmonary and extrapulmonary cryptococcal disease have a lumbar puncture per-formed to rule out concomitant central nervous system (CNS) infection. Immunocompetent patients who are asymptomatic and who have a culture of the lung that is positive for Cryptococcus neoformans may be observed carefully or treated with fluconazole, 200-400 mg/day for 3-6 months (Dismukes et al., 1987; Dromer et al., 1996; Yamaguchi et al., 1996; Pappas, et al., 1998) (AIII). Immunocompetent patients who present with mild-to-moderate symptoms should be treated with fluconazole, 200-400 mg/day for 6-12 months (Dismukes et al., 1987; Dromer et al., 1996) (AIII). In cases where fluconazole is not an option, an acceptable alternative regimen is itraconazole, 200-400 mg/ day, for 6-12 months (Denning et al., 1989) (BIII). The toxicity of amphotericin B limits its utility as a desired agent in the treatment of mild-to-moderate pulmonary disease among immunocompetent hosts. However, if oral azole therapy cannot be given, or the pulmonary disease is severe or progressive, amphotericin B is recommended, 0.4-0.7 mg/kg/day for a

total dose of 1000-2000 mg (BIII). Ketoconazole has in vitro activity against Cryptococcus neoformans, but is generally ineffective in the treatment of cryptococcal meningitis and should be used rarely, if at all, in this setting (Dismukes et al., 1983) (CIII). Some reports describe the successful use of flucytosine (100 mg/kg/day for 6–12 months) as therapy for pulmonary cryptococcal disease; however, concern about the development of resistance to flucytosine when used alone limits its use in this setting (Utz et al., 1968; Kerkering, Duma & Shadomy, 1981) (DII). Immunocompromised patients with non-central nervous system pulmonary and extrapulmonary disease should be treated in the same fashion as patients with central nervous system disease (Dromer et al., 1996; Yamaguchi et al., 1996) (AIII).

Some patients present with isolated cryptococcemia, a positive serum cryptococcal antigen titer (greater than 1:8) without evidence of clinical disease, or a positive urine culture or prostatic disease. Although no retrospective or prospective studies have been conducted to investigate treatment options for such patients, they should probably be treated with antifungal therapy (AIII).

Central Nervous System Disease

Specific recommendations for the treatment of non-HIV-associated cryptococcal meningitis are summarized in Table 1 of the original guideline document. Combination therapy of amphotericin B and flucytosine will sterilize cerebral spinal fluid within 2 weeks of treatment in 60%-90% of patients. Most immunocompetent patients will be treated successfully with 6 weeks of combination therapy (Bennett et al., 1979; Dismukes et al., 1987) (AI); however, owing to the requirement of intravenous therapy for an extended period of time and the relative toxicity of the regimen, alternatives to this approach have been advocated. Despite the absence of controlled clinical trial data from HIV-negative populations of patients, a frequently used alternative treatment for cryptococcal meningitis in immunocompetent patients is an induction course of amphotericin B (0.5-1 mg/ kg/day) with flucytosine (100 mg/kg/day) for 2 weeks, followed by consolidation therapy with fluconazole (400 mg/day) for an additional 8-10 weeks (Pappas et al., 1998) (BIII). This recommendation is extrapolated from the treatment experience of patients with HIV-associated cryptococcal meningitis (van der Horst et al., 1997; Saag et al., 1992). Pilot studies that have investigated fluconazole with flucytosine as initial therapy yielded unsatisfactory outcomes. Therefore, initial therapy with fluconazole, even among "low risk" patients, is discouraged (DIII). A lumbar puncture is recommended after 2 weeks of treatment to assess the status of cerebral spinal fluid sterilization. Patients with a positive culture at 2 weeks may require a longer course of induction therapy. Also, it is optional to continue fluconazole (200 mg/day) for 6-12 months (BIII).

Immunosuppressed patients, such as solid organ transplant recipients, require more prolonged therapy. On the basis of experience of treating cryptococcal meningitis in HIV disease, it is reasonable to follow a similar induction, consolidation, and suppression strategy, since previous strategies reported failure rates of 15%-20% with 6 weeks of treatment with combination amphotericin B/5-flucytosine (Dismukes, et al., 1987). Therapy with amphotericin B (0.7-1 mg/kg/day) for 2 weeks, followed by 8-10 weeks of fluconazole (400-800 mg/day), is followed with 6-12 months of suppressive therapy with a lower dose

of fluconazole (200 mg/day) (BIII). For those patients receiving long-term prednisone therapy, reduction of the prednisone dosage (or its equivalent) to 10 mg/day, if possible, may result in improved outcome to antifungal therapy.

For both immunocompetent and immunocompromised patients with significant renal disease, lipid formulations of amphotericin B may be substituted for amphotericin B during the induction phase (Leenders et al., 1997) (CIII). For patients who are unable to tolerate fluconazole, itraconazole (200 mg twice daily) may be substituted (CIII). Most parenchymal lesions will respond to antifungal treatment; large (13 cm) accessible central nervous system lesions may require surgery. All patients should be monitored closely for evidence of elevated intracranial pressure and managed in a fashion similar to HIV-positive patients. Treatment decisions should not be based routinely or exclusively on cryptococcal polysaccharide antigen titers in either the serum or cerebral spinal fluid (Powderly et al., 1994; Tuazon et al., 1998) (AI). Because the goal is cure following cessation of therapy, patients requiring suppressive therapy for greater than 1-2 years should be considered failures. Intrathecal or intraventricular amphotericin B may be used in refractory cases where systemic administration of antifungal therapy has failed. Owing to its inherent toxicity and difficulty of administration, this therapy is recommended only in this salvage setting (Polsky et al., 1986) (CII).

Guidelines for the Treatment of Pulmonary and Central Nervous System Cryptococcosis in Patients with HIV Infection

Therapy for Acquired Immune Deficiency Syndrome (AIDS)-Related Cryptococcal Pneumonia

Specific recommendations for the treatment of HIV-associated cryptococcal pulmonary disease are summarized in Table 2 of the original guideline document. Patients who present with mild-to-moderate symptoms or who are asymptomatic with a positive culture for Cryptococcus neoformans from the lung should be treated with fluconazole, 200-400 mg/day for life (Dismukes et al., 1987; Dromer et al., 1996; Jones et al., 1991) (AII); however, long-term follow-up studies on the duration of treatment in the era of highly active antiretroviral therapy (HAART) are needed. In cases where fluconazole is not an option, an acceptable alternative is itraconazole, 400 mg/day for life (Denning et al., 1989) (CII). A potential treatment option is combination therapy with fluconazole, 400 mg/day, plus flucytosine, 150 mg/kg/day, for 10 weeks; however, the toxicity associated with this regimen limits its utility (CII). In patients with more severe disease, amphotericin B should be used until symptoms are controlled, then an oral azole agent, preferably fluconazole, can be substituted (BIII). Ketoconazole is generally ineffective in the treatment of cryptococcosis in HIV-infected patients and should probably be avoided (Dismukes et al., 1983; Chuck & Sande, 1989) (DII).

Therapy for AIDS-Related Cryptococcal Meningitis

A summary of treatment recommendations for AIDS-associated cryptococcal meningitis is provided in Table 2 of the original guideline document. Amphotericin B (0.7–1 mg/kg given intravenous daily for greater than 2 weeks) combined with flucytosine, 100 mg/kg given orally in 4 divided doses per day, is the initial

treatment of choice (van der Horst et al., 1997; Saag et al., 1992; Larsen, Leal, & Chan, 1990; White et al., 1992) (AI). In cases where flucytosine cannot be administered, amphotericin B alone (administered at the same doses listed above) is an acceptable alternative (Saag et al., 1992) (BI). After the 2-week period of successful induction therapy, consolidation therapy should be initiated with fluconazole (400 mg orally once daily) administered for 8 weeks or until cerebral spinal fluid (CSF) cultures are sterile (van der Horst et al., 1997) (AI). In cases where fluconazole cannot be given, itraconazole is an acceptable, albeit less effective, alternative (Denning et al., 1989; de Gans et al., 1992) (BI). Lipid formulations of amphotericin B appear beneficial and may be useful for patients with cryptococcal meningitis and renal insufficiency (Leenders et al., 1997; Larsen, Leal & Chan, 1990; Coker et al., 1993; Diamond et al., 1998; Denning et al., 1991) (CII). The optimal dose of lipid formulations of amphotericin B has not been determined, but AmBisome has been effective at doses of 4 mg/kg/day (Leenders et al., 1997). Combination therapy with fluconazole (400–800 mg/day) and flucytosine (100 mg/kg/day in 4 divided doses) has been shown to be effective in the treatment of AIDS-associated cryptococcal meningitis (Larsen et al., 1994; White et al., 1992). However, owing to the toxicity of this regimen, it is recommended only as an alternative option for therapy (Larsen et al., 1994) (CII). Intrathecal or intraventricular amphotericin B may be used in refractory cases where systemic administration of antifungal therapy has failed. Owing to its inherent toxicity and difficulty of administration, it is recommended only in a salvage setting (Polsky et al., 1986) (CII).

In selected cases, susceptibility testing of the Cryptococcus neoformans isolate may be beneficial to patient management, particularly if a comparison can be determined between baseline and sequential isolates. Such testing is generally best used in cases of relapse or in cases of refractory disease. At this time, susceptibility testing of isolates is not recommended for routine patient care (CIII).

Maintenance Therapy for AIDS-Associated Cryptococcal Meningitis

Aggressive antiretroviral therapy should be administered in accordance with standards of care in the community (Carpenter et al., 1998). In conjunction with antiretroviral therapy, long-term maintenance antifungal therapy should be administered. Oral fluconazole, 200 mg/day, is the most effective maintenance therapy for AIDS-associated cryptococcal meningitis (Saag et al., 1999; Powderly et al., 1992) (AI). A randomized comparative trial demonstrated the superiority of fluconazole (200 mg/day) over amphotericin B (1 mg/kg/week) as maintenance therapy. Patients in the amphotericin B group had significantly more relapses, more drug-related adverse events, and more bacterial infections, including bacteremia. Relapse rates were 2% for fluconazole and 17% for amphotericin B. Therefore, owing to its toxicity and difficulty with administration, amphotericin B maintenance therapy should be reserved for those patients who have had multiple relapses while receiving azole therapy or who are intolerant of the azole agents (CI). In another randomized comparative trial, fluconazole was demonstrated to be superior to itraconazole as maintenance therapy for cryptococcal disease (Saag et al., 1999). This trial was terminated by an independent data safety monitoring board after preliminary results revealed a cerebral spinal fluid culture relapse rate of 4% among patients receiving fluconazole (200 mg/day), compared with 24% relapse among itraconazole (200 mg/day) recipients. Thus, itraconazole should be

used in cases where the patient is intolerant of fluconazole or has failed fluconazole therapy (BI). It may be prudent to use doses of 200 mg of itraconazole twice daily (BIII). Ketoconazole is not effective as maintenance therapy (Chuck & Sande, 1989) (DII). Although some preliminary evidence suggests lower relapse rates of opportunistic infections when patients have been successfully treated with potent antiretroviral therapy, until proven otherwise, maintenance therapy for cryptococcal meningitis should be administered for life (AI). For selected patients who have responded very well to highly active antiretroviral therapy (HAART), consideration might be given to discontinuing secondary antifungal prophylaxis after 12–18 months of successful suppression of HIV viral replication (CIII).

Management of Elevated Intracranial Pressure

The principal intervention for reducing elevated intracranial pressure is percutaneous lumbar drainage (Denning et al., 1991; Graybill et al., 1997) (AII). Radiographic imaging of the brain is recommended prior to performance of the initial lumbar puncture to rule out the presence of a space-occupying lesion (Denning et al., 1991) (BII). Among patients with normal baseline opening pressure (<200 mm H_2O), a repeat lumbar puncture should be performed 2 weeks after initiation of therapy to exclude elevated pressure and to evaluate culture status. For patients with elevated baseline opening pressure, lumbar drainage should remove enough cerebral spinal fluid to reduce the opening pressure by 50%. Patients should initially undergo daily lumbar punctures to maintain cerebral spinal fluid opening pressure in the normal range. When the cerebral spinal fluid pressure is normal for several days, the procedure can be suspended. Occasionally patients who present with extremely high opening pressures (>400 mm H_2O) may require a lumbar drain, especially when frequent lumbar punctures are required to or fail to control symptoms of elevated intracranial pressure. In cases where repeated lumbar punctures or use of a lumbar drain fail to control elevated pressure symptoms, or when persistent or progressive neurological deficits are present, a ventriculoperitoneal shunt is indicated (Denning et al., 1991; Graybill et al., 1997) (BII).

Treatment with steroids has yielded mixed results in both HIV-infected and HIV-negative patients, and its impact on outcome is unclear. Owing to the intense fungal burden and large amount of replication in patients with HIV disease, adjunctive steroid therapy is not recommended for HIV-infected patients (DIII). Among HIV-negative patients, the benefit of steroid therapy is not well-established and should not be used (DIII). Acetozolamide and mannitol have not been shown to provide any clear benefit in the management of elevated intracranial pressure resulting from cryptococcal meningitis (DIII).

Definitions of Strength of Recommendation and Quality of Evidence Ratings:

Quality of evidence:

I. Evidence from at least one properly randomized, controlled trial
II. Evidence from at least one well-designed clinical trial without randomization, from cohort or case-control analytic studies (preferably from more than one

center), from multiple time-series studies, or from dramatic results of uncontrolled experiments

III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

Strength of recommendation:

A. Good evidence to support a recommendation for use
B. Moderate evidence to support a recommendation for use
C. Poor evidence to support a recommendation
D. Moderate evidence to support a recommendation against use
E. Good evidence to support a recommendation against use

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Early, appropriate treatment of non-central nervous system (CNS) pulmonary and extrapulmonary cryptococcosis reduces morbidity and prevents progression to potentially life-threatening central nervous system disease.
- Early, appropriate treatment of both HIV-associated and non-HIV-associated cryptococcal meningitis reduces both morbidity and mortality.
- Prevention of relapse of cryptococcosis reduces mortality and morbidity and slows the progression of HIV disease.
- Aggressive management of elevated intracranial pressure helps to reduce mortality and minimize morbidity resulting from acute cryptococcal meningitis.

Subgroups Most Likely to Benefit:

Patients with solid organ transplants will benefit from aggressive treatment of early cryptococcal disease which may prevent the loss of the transplanted organ.

POTENTIAL HARMS

- Drug-related toxicities and development of adverse drug-drug interactions are the principal potential harms of therapeutic intervention.
- Toxic side effects of amphotericin B are common and include nausea, vomiting, chills, fever, and rigors, which can occur with each dose. The most troublesome toxic side effect is renal injury, including elevation of the serum creatinine, hypokalemia, hypomagnesemia, and renal tubular acidosis. In addition, anemia occurs frequently and thrombocytemia occurs occasionally (possibly as a result of exposure to heparin). It is necessary to carefully monitor serum electrolytes, renal function, and bone marrow function. Nevertheless, amphotericin B can be employed safely and effectively; only 3% of patients will have toxic side effects of a magnitude that requires it to be discontinued within the first 2 weeks of therapy.
- There are considerable side effects from flucytosine when given in combination with fluconazole for 10 weeks in patients with HIV-associated cryptococcal meningitis. Dose-limiting adverse effects (predominantly gastrointestinal in nature) that resulted in the discontinuation of flucytosine were reported in 28% of patients; and another 32% described significant side effects that did not result in the discontinuation of therapy.
- Abdominal pain, nausea, and skin rash are the most common adverse effects of fluconazole.
- The main risk of lumbar drainage occurs in the setting of a coexistent mass lesion and obstructive hydrocephalus, which is a relatively rare complication of cryptococcal disease. Prolonged external lumbar drainage places patients at major risk for bacterial infection. Ventriculoperitoneal shunts may become secondarily infected with bacteria; however, this is an uncommon complication. Secondary infection of the shunt with Cryptococcus neoformans generally does not occur if antifungal therapy has been instituted.
- Drug acquisition costs are high for antifungal therapies administered for long periods of time (6 months to life). Additional costs are accrued for frequent monitoring (weekly, monthly, etc.) and supervision of therapies associated with most of the recommended regimens.

Subgroups Most Likely to Be Harmed:

- Patients taking amphotericin B or flucytosine or fluconazole/flucytosine in combination
- Patients with coexistent mass and hydrocephalus
- Patients receiving prolonged external lumbar drainage
- Patients with ventriculoperitoneal shunts

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Saag MS, Graybill RJ, Larsen RA, Pappas PG, Perfect JR, Powderly WG, Sobel JD, Dismukes WE. Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. Clin Infect Dis 2000 Apr;30(4):710-8. [37 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2000 Apr

GUIDELINE DEVELOPER(S)

Infectious Diseases Society of America - Medical Specialty Society

SOURCE(S) OF FUNDING

Infectious Diseases Society of America (IDSA)

GUIDELINE COMMITTEE

Infectious Diseases Society of America (IDSA) Practice Guidelines Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Authors: Michael S. Saag, Richard J. Graybill, Robert A. Larsen, Peter G. Pappas, John R. Perfect, William G. Powderly, Jack D. Sobel, and William E. Dismukes for the Mycoses Study Group Cryptococcal Subproject (Mycoses Study Group Cryptococcal Subcommittee of the National Institute of Allergy and Infectious Diseases [NIAID] Mycoses Study Group)

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

An update is not in progress at this time.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Infectious Diseases Society of America (IDSA) Web site. Also available in HTML format.

Print copies: Available from the University of Chicago Press; fax: (773) 702-6096.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Kish MA. Guide to development of practice guidelines. Clinical Infectious Diseases 2001;32:851-4.
- Gross PA. Practice guidelines for infectious diseases: Rationale for a work in progress. Clin Infect Dis. 1998 May;26(5):1037-41.
- Gross PA, Barrett TL, Dellinger EP, Krause PJ, Martone WJ, McGowan JE Jr, Sweet RL, Wenzel RP. Purpose of quality standards for infectious diseases. Infectious Diseases Society of America. Clin Infect Dis 1994 Mar;18(3):421.

Electronic copies: Available from the Infectious Diseases Society of American (IDSA) Web site.

Print copies: Available from Infectious Diseases Society of America, 66 Canal Center Plaza, Suite 600, Alexandria, VA 22314.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on May 1, 2001. The information was verified by the guideline developer as of June 29, 2001.

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